

Harry Goldblatt and the discovery of renin

In 1934, pathologist Harry Goldblatt established the first animal model of hypertension. This model provided researchers with the tools to delineate the renin-angiotensin system of blood pressure control and, eventually, to design enzyme inhibitors for the treatment of chronic hypertension.

As early as the mid-19th century, physicians had noted that patients with kidney disease and those with long-term high blood pressure (hypertension) both had enlarged heart muscles. The first clue to this kidney-hypertension connection came from physiologists Robert Tigerstedt and Per Bergman who injected kidney extracts into rabbits, thus triggering a dramatic rise in blood pressure. In a prophetic explanation, they suggested that the kidneys produced a soluble protein—they called it renin—that triggered a rise in blood pressure (1).

A little help from man's best friend

Decades later, the duo's results prompted attempts to provoke hypertension by stressing or injuring the kidneys of animals. None were successful until Harry Goldblatt arrived on the scene. Goldblatt had noted a characteristic narrowing of the renal blood vessels in patients who had died of hypertension. He reasoned that a decreased blood flow, and thus oxygen supply, to the kidneys (ischemia) might somehow trigger hypertension.

To test this idea, Goldblatt partially constricted the major renal arteries of dogs using a self-styled adjustable silver clamp. Partial constriction of both renal arteries resulted in a reproducible and persistent rise in blood pressure, in the absence of overt renal failure. Clamping other large arteries—splenic or femoral—had no effect, indicating that hypertension resulted specifically from kidney ischemia. Goldblatt published these results in 1934 in the *Journal of Experimental Medicine* (2).

Goldblatt's explanation for his results was similar to that of Tigerstedt and Bergman: ischemia causes the kidneys to produce an "internal secretion" that triggers vasoconstriction. This idea met with

considerable skepticism. "Goldblatt's discovery was spectacular, but nobody believed it," recalls cardiologist John Laragh. The skepticism, Laragh says, was largely because of the technical difficulty of Goldblatt's procedure, which few could reproduce. Eventually, Goldblatt's results were confirmed, but determining the identity of the "internal secretion" and renin (one and the same) took many more years.

The hunt for renin

Two groups—one led by Eduardo Braun-Menendez and the other by Irvine Page—attempted to purify renin but found that the higher the purity of the extract the less hypertensive activity it had. This confusing result was eventually explained by the discovery, in 1939, that the pressure-raising substance was not renin itself. Rather, renin was a proteolytic enzyme that converted a plasma peptide into a hypertensive product. Purifying renin away from its substrate had abolished its activity.

The two groups christened the active peptide product of renin "hypertensin"

and "angiotonin," respectively (3, 4). They later compromised and renamed it "angiotensin" and its precursor "angiotensinogen" (5). Leonard Skeggs and colleagues later discovered that there were two forms of angiotensin (6), and it is now known that renin initiates an enzymatic cascade in which angiotensinogen is converted into angiotensin I, which is then processed by angiotensin-converting enzyme (ACE) into angiotensin II. Angiotensin II is the true culprit of hypertension.

Renin in human hypertension

Simple theory would predict high renin levels in patients with hypertension, but instead, says Laragh, "renin levels are all over the place." Thus, despite an understanding of the renin-angiotensin system in animals, there was still doubt about its role in humans. The development of ACE inhibitors helped explain this seeming inconsistency. Laragh and colleagues injected the first such inhibitor into patients and found a drop in blood pressure, but only in patients with high levels of circulating renin (7). In other studies, Laragh showed that hypertension not caused by increased renin results from insufficient salt excretion by the kidney (8). The work of Laragh and others thus revealed that hypertension is not a single mechanistic process, but still confirmed Goldblatt's original idea: production of renin by the kidney regulates blood pressure.

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Harry Goldblatt, 1964. Image provided by the National Library of Medicine.

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